Management of Diabetes Mellitus in Chronic Kidney Disease

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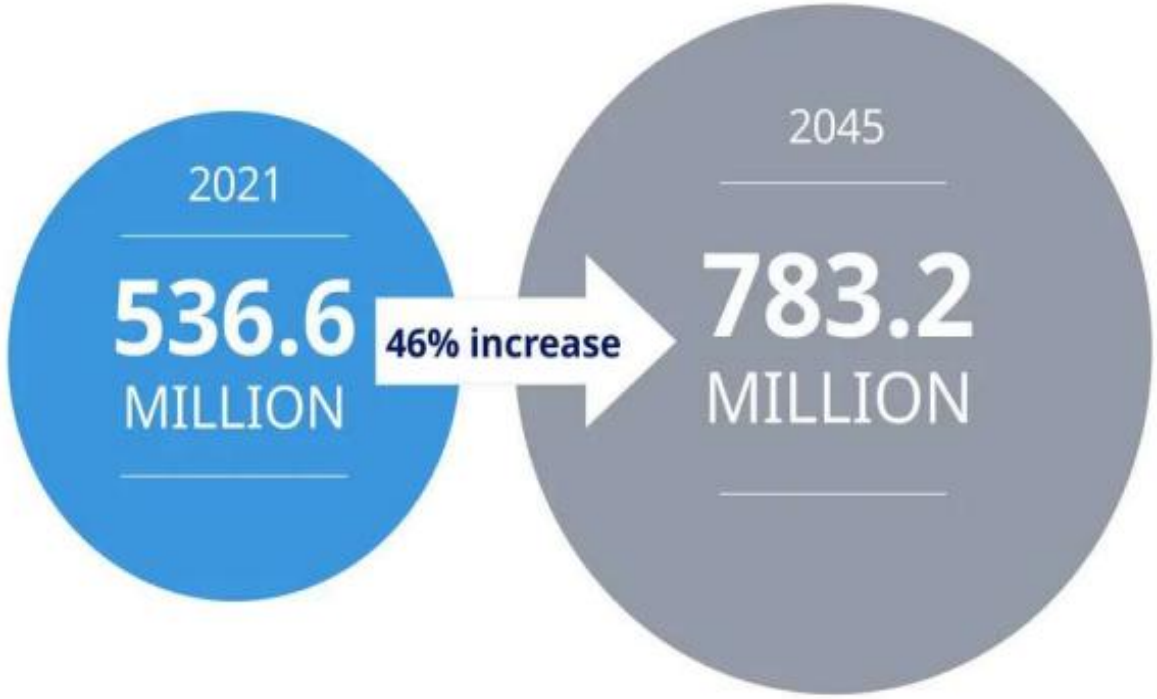
AWMC

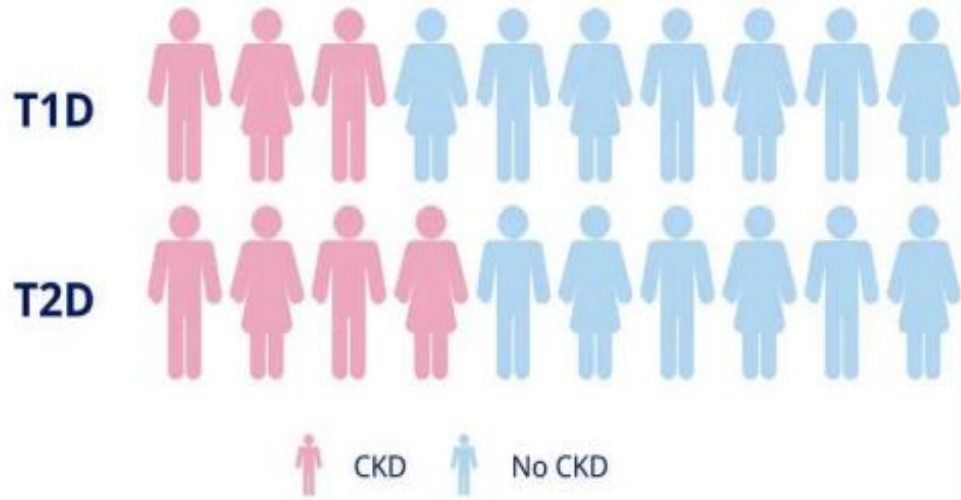
CKD is a common complication of T2D

With significant disease burden

Growing global incidence of diabetes in adults aged 20–79 years[1]



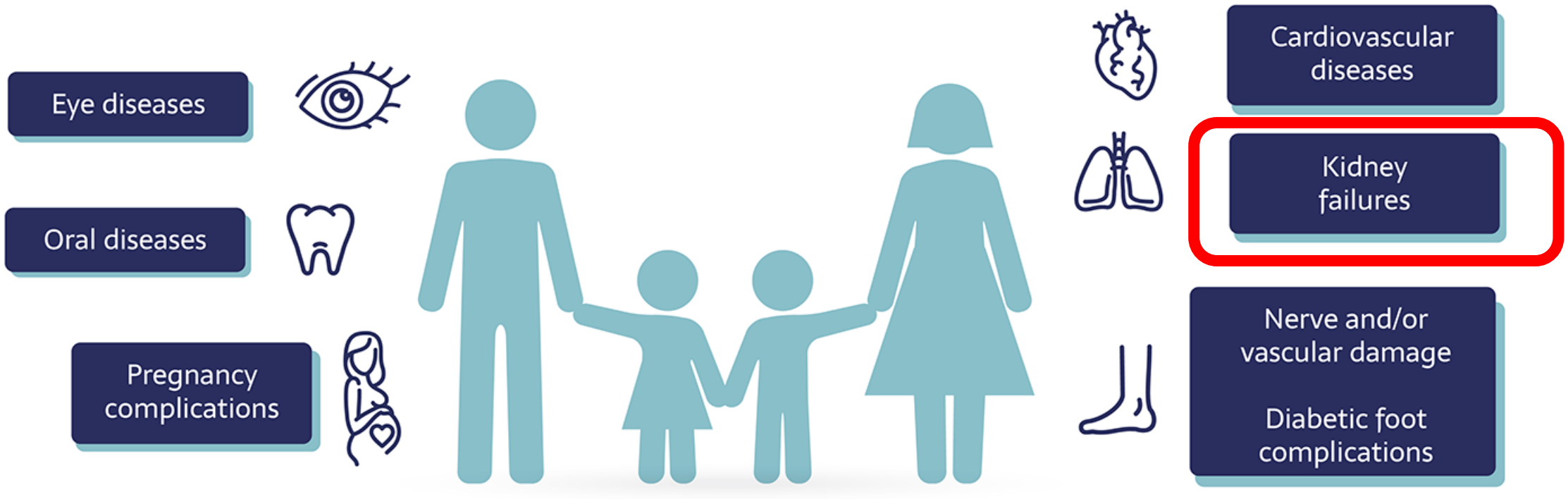
CKD is common in diabetes[2]



CKD, chronic kidney disease; T1D, type 1 diabetes; T2D, type 2 diabetes. 1. Sun H et al. International Diabetes Federation. IDF Diabetes Atlas. Diabetes Research and Clinical Practice. 2022; 183:109119 Available at IDF Diabetes Atlas: Global, regional and country-level diabetes prevalence estimates for 2021 and projections for 2045 – ScienceDirect; 2. Alicic RZ et al. Clin J Am SoNc ephrol 2017;12:2032-2045

FLOW
semaglutide | renal outcomes trial

Major DIABETES complications



IDF, 2020

CKD in Diabetes:

CKD
in Diabetes

=

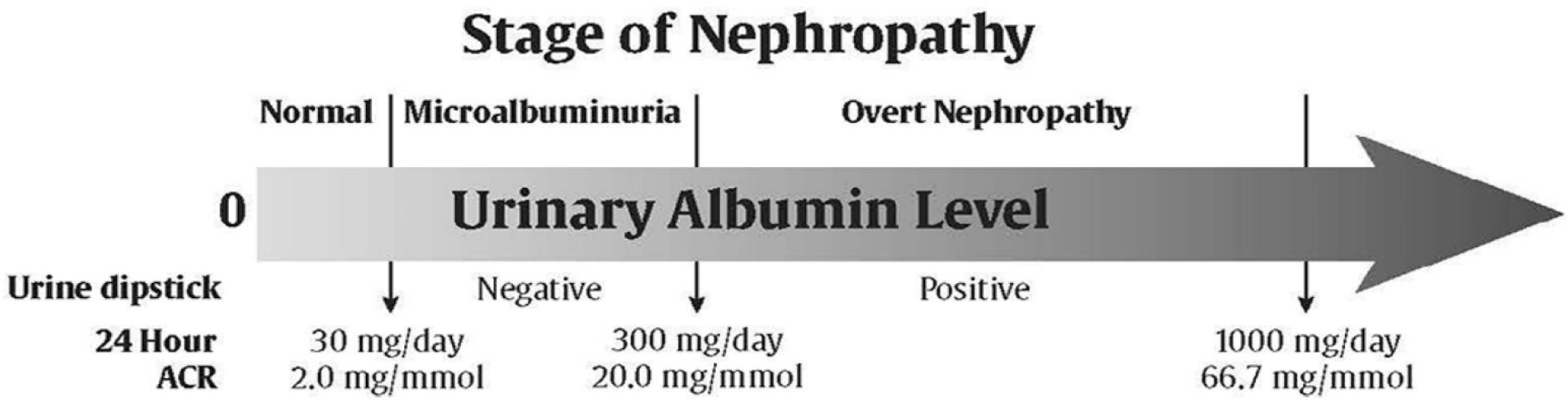
ACR ≥2.0 mg/mmol

and / or

eGFR <60 mL/min/1.73 m2

ACR, albumin to creatinine ratio; *CKD*, chronic kidney disease; *eGFR*, estimated glomerular filtration rate

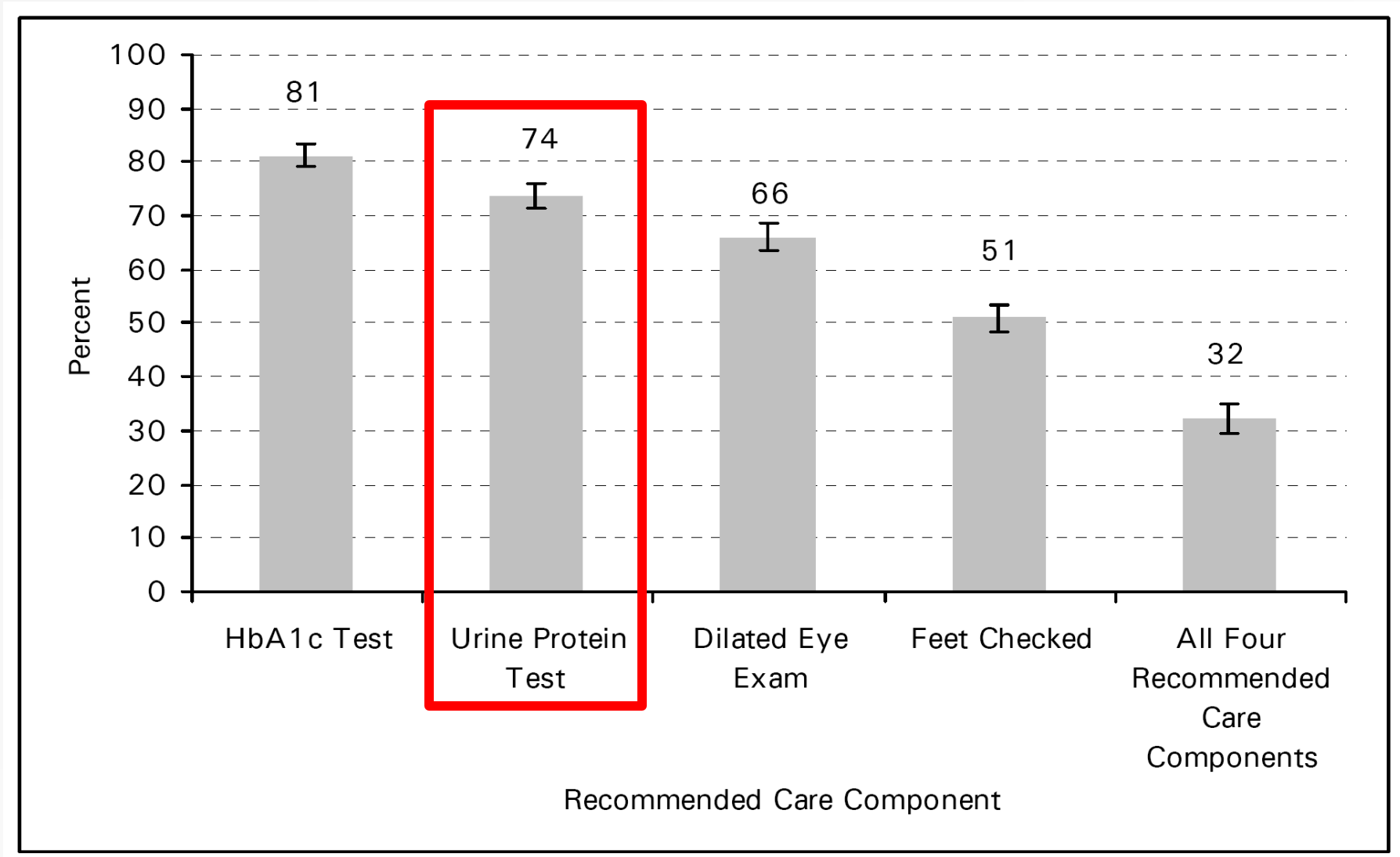
Stage of Nephropathy:



Stages of Diabetic Nephropathy by Level of Urinary Albumin Level			
Stage of nephropathy	**Urine dipstick for protein**	**Urine ACR (mg/mmol)**	**24 hour urine collection for albumin**
Normal	Negative	<2	<30 mg/day
Microalbuminuria	Negative	2–20	30–300 mg/day
Overt nephropathy	Positive	>20 >67	>300 mg/day >1000 mg/day
Values are for urinary albumin, not total urinary protein, which will be higher than urinary albumin levels. ACR results may be elevated with conditions other than diabetic nephropathy (see text and Table 3)			

ACR, albumin to creatinine ratio.

Care Gap Still Exists for Screening:



Glycemic targets and Glycemic status monitoring in CKD patients

Glycemic monitoring and targets in patients with diabetes and CKD

- An individualized HbA1c target ranging from <6.5% to <8.0% in patients with diabetes and CKD not treated with dialysis.
- For patients for whom prevention of complications is the key goal, a lower HbA1c target (e.g., <6.5% or <7.0%) might be preferred.

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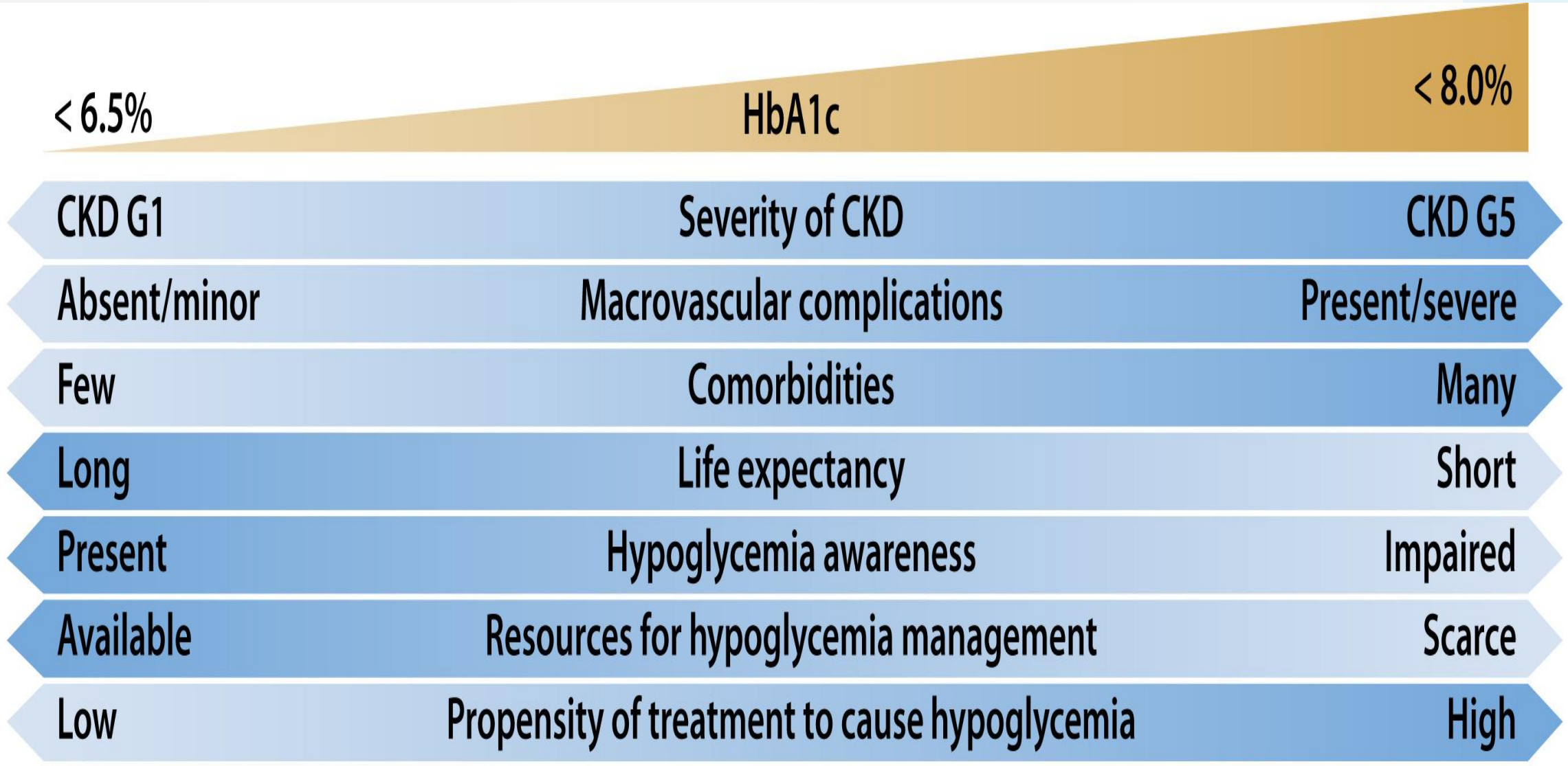
Glycemic monitoring and targets in patients with diabetes and CKD:

- For those with multiple comorbidities or increased burden of hypoglycemia, a higher HbA1c target (e.g., <7.5% or <8.0%) might be preferred.
- When the eGFR is <30ml/min/1.73 m^2, the HbA1c measures 0.5% to 1.0% lower than it should, a rule of thumb estimate could be to add this amount to the measured HbA1c to get an idea of **true HbA1c.**

Kidney International 2020 98S1-S115DOI: (10.1016/j.kint.2020.06.019)

Frequency of glycated hemoglobin (HbA1c) measurement and use of glucose management indicator (GMI) in hronic kidney disease (CKD)

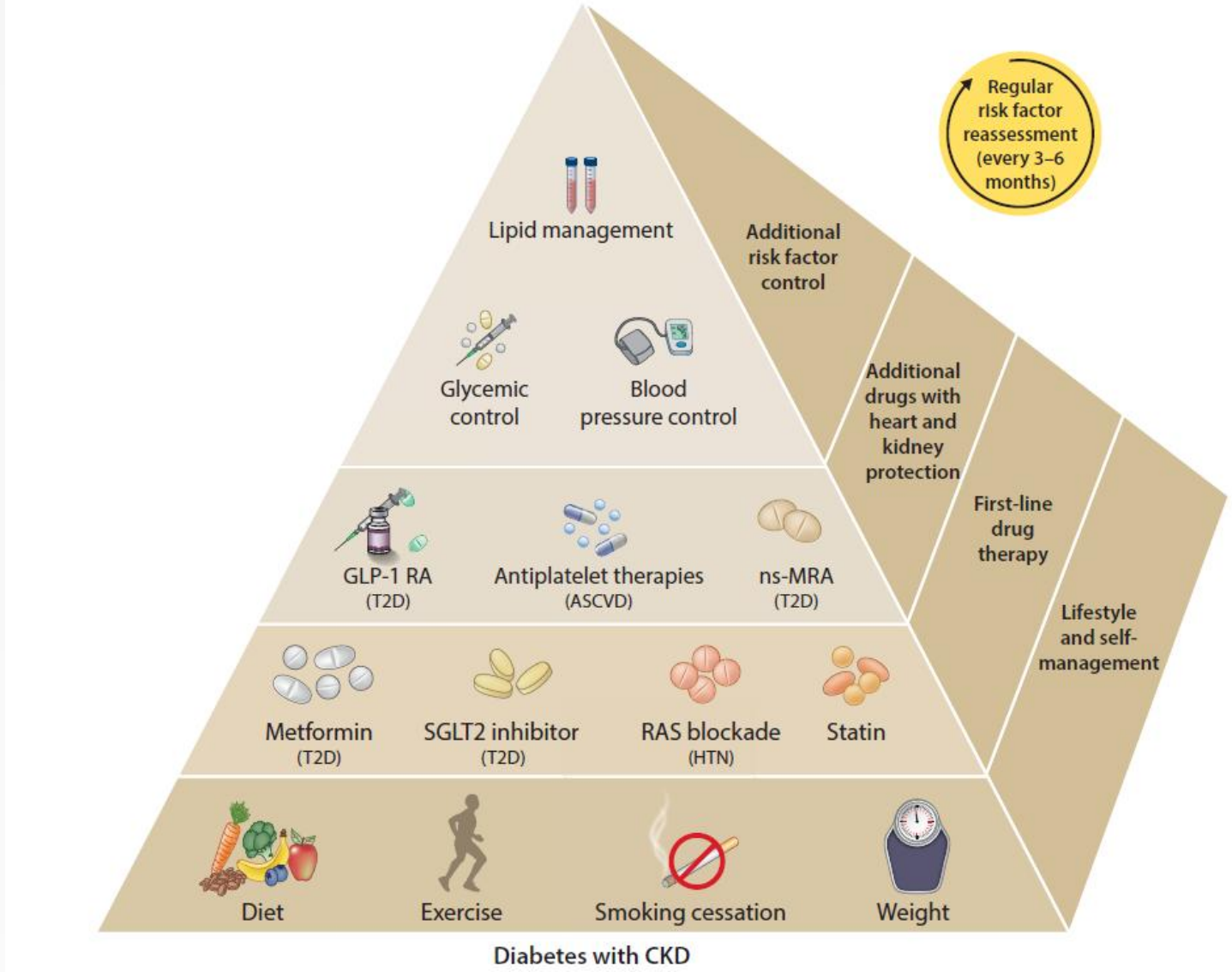
Population	HbA1c			GMI
	Measure	Frequency	Reliability	
CKD G1–G3b	Yes	• Twice per year • Up to 4 times per year if not achieving target or change in therapy	High	Occasionally useful
CKD G4–G5 including treatment by dialysis or kidney transplant	Yes	• Twice per year • Up to 4 times per year if not achieving target or change in therapy	Low	Likely useful

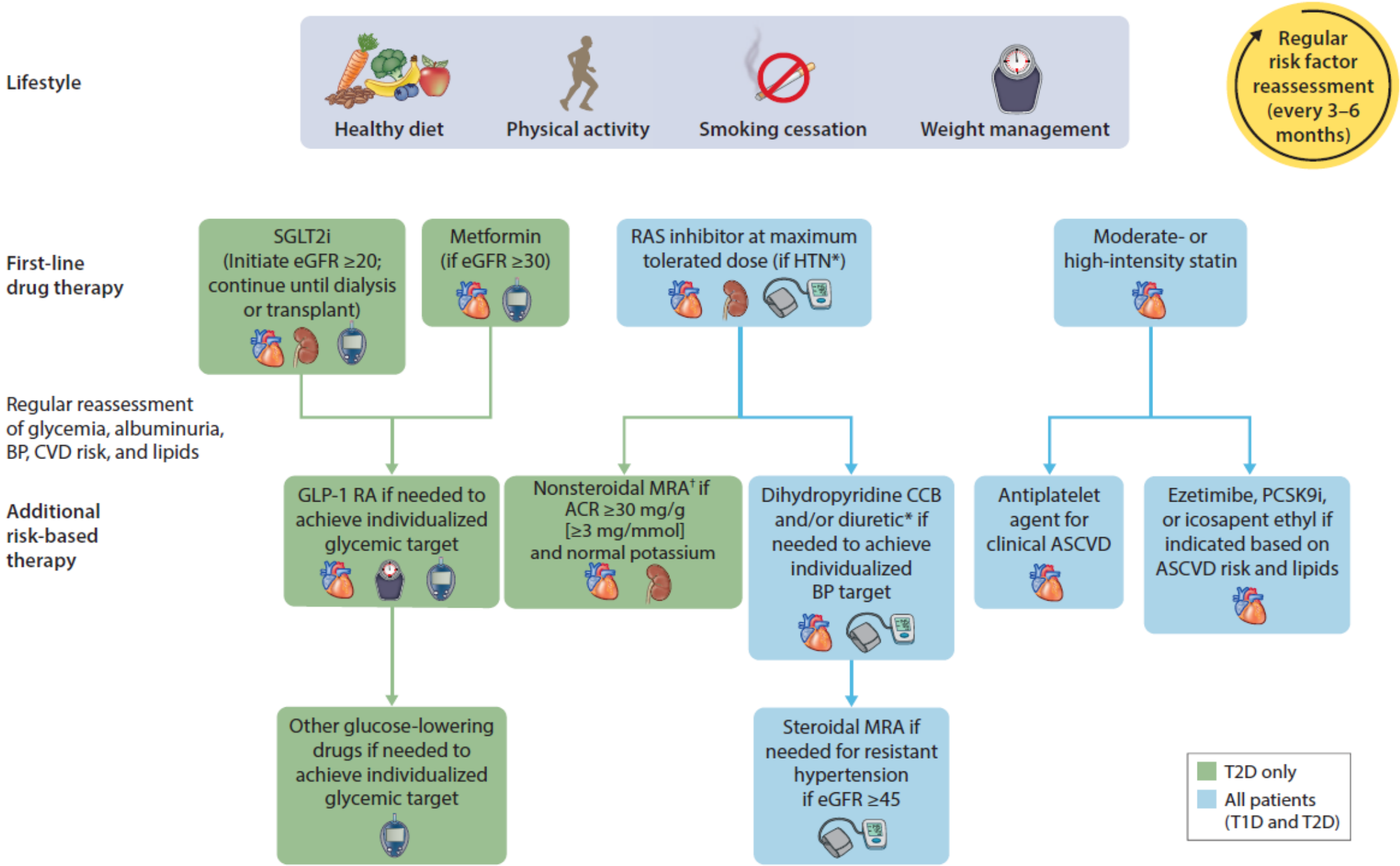

< 6.5%
HbA1c
< 8.0%
CKD G1
Severity of CKD
CKD G5
Absent/minor
Macrovascular complications
Present/severe
Few
Comorbidities
Many
Long
Life expectancy
Short
Present
Hypoglycemia awareness
Impaired
Available
Resources for hypoglycemia management
Scarce
Low
Propensity of treatment to cause hypoglycemia
High

Diabetes Management in CKD Patients

Comprehensive diabetes and CKD management

Patients with diabetes and chronic kidney disease (CKD) should be treated with a comprehensive strategy to reduce risks of kidney disease progression and cardiovascular disease





Holistic approach for improving outcomes in patients with diabetes and chronic kidney disease.

Lifestyle Interventions

Lifestyle interventions in patients with diabetes and CKD:

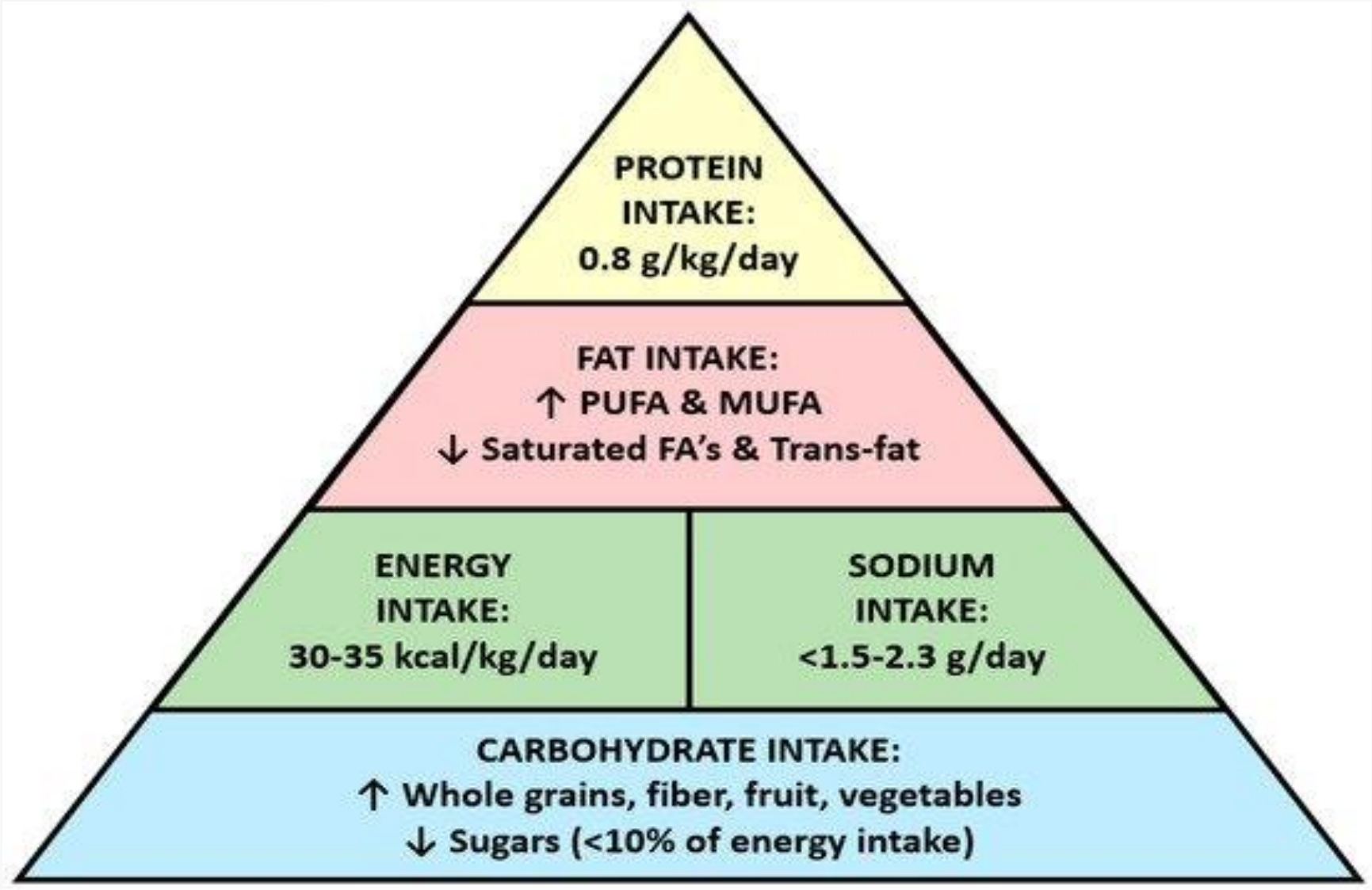
- Patients with diabetes and CKD be advised to undertake moderate-intensity physical activity for a cumulative duration of at least 150 minutes per week, or to a level compatible with their cardiovascular and physical tolerance
- Maintaining a protein intake of 0.8 g protein/kg (weight)/d for those with diabetes and CKD not treated with dialysis

Lifestyle interventions in patients with diabetes and CKD:

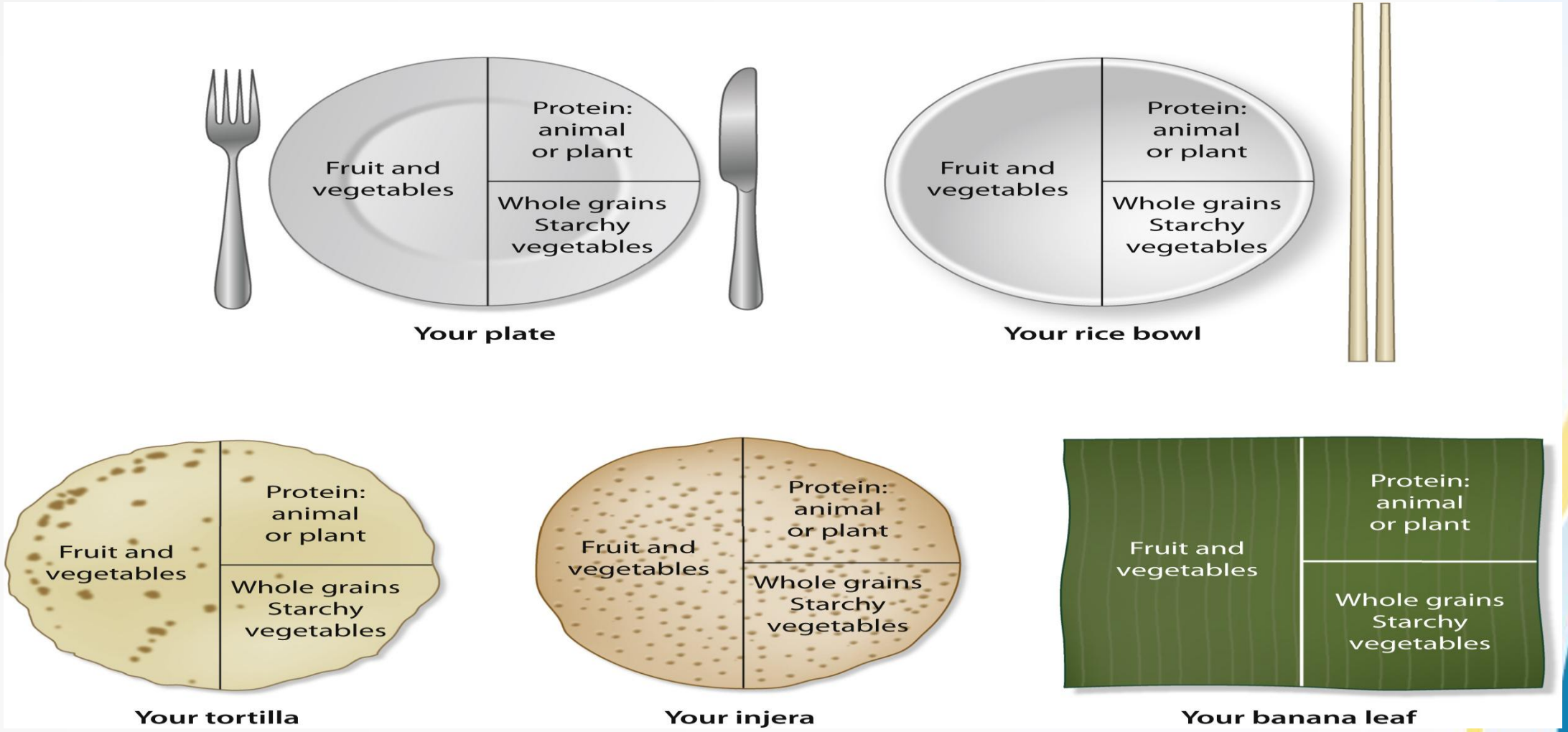
- Sodium intake be <2 g of sodium per day (or <90 mmol of sodium per day, or <5 g of sodium chloride per day) in patients with diabetes and CKD

Weight (kg)	35	40	50	55	60	65	70	75	80	85	90	95	100
Grams of protein per day (wt x 0.8 g/kg)	28	32	40	44	48	52	56	60	64	68	72	76	80

DKD Food Pyramid



Lifestyle interventions in patients with diabetes and CKD



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Smoking cessation

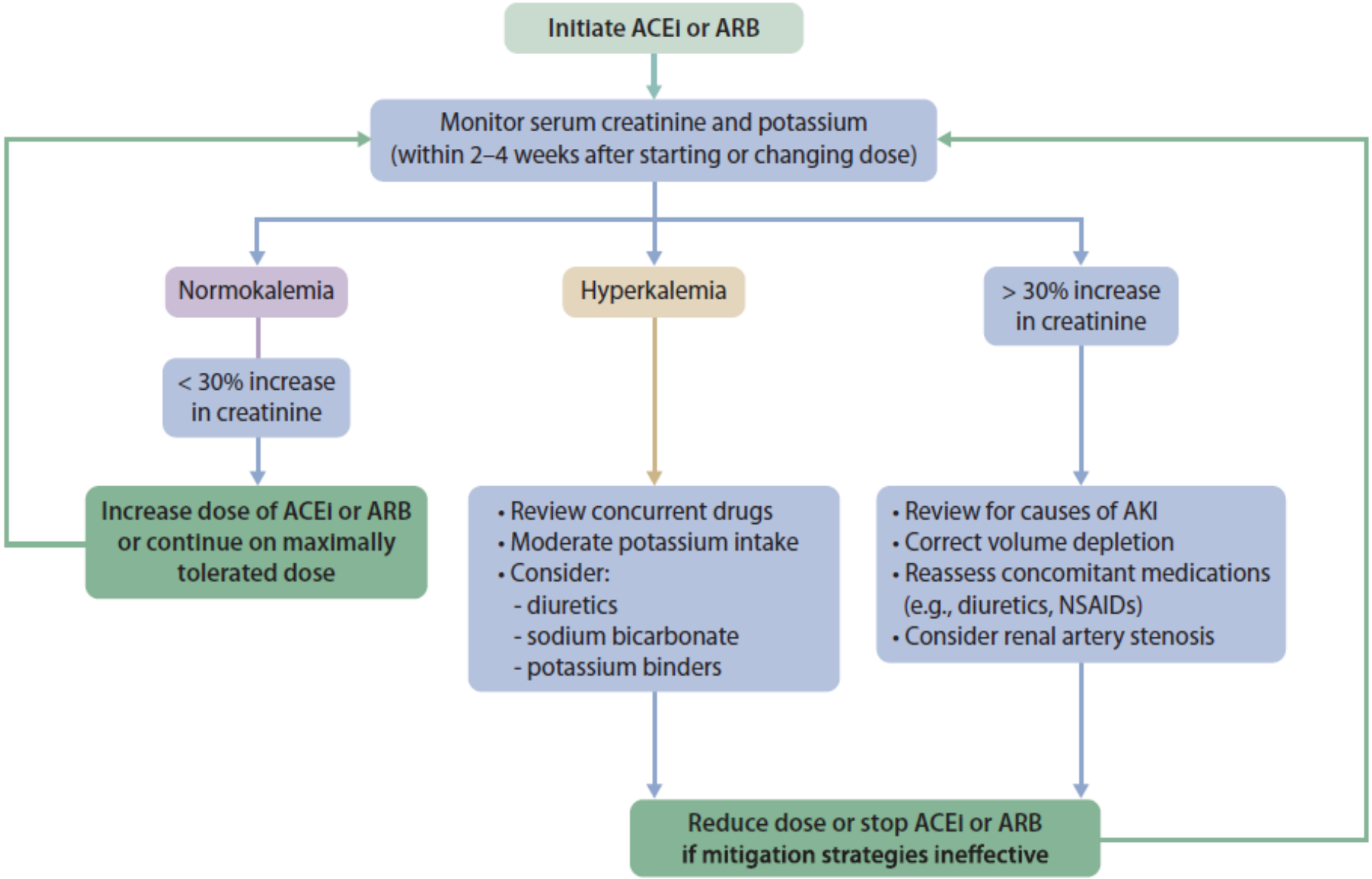
- KDIGO recommends advising patients with diabetes and CKD who use tobacco to quit using tobacco products

- Physicians should counsel patients with diabetes and CKD to reduce second hand smoke exposure.

Renin–angiotensin system (RAS) blockade:

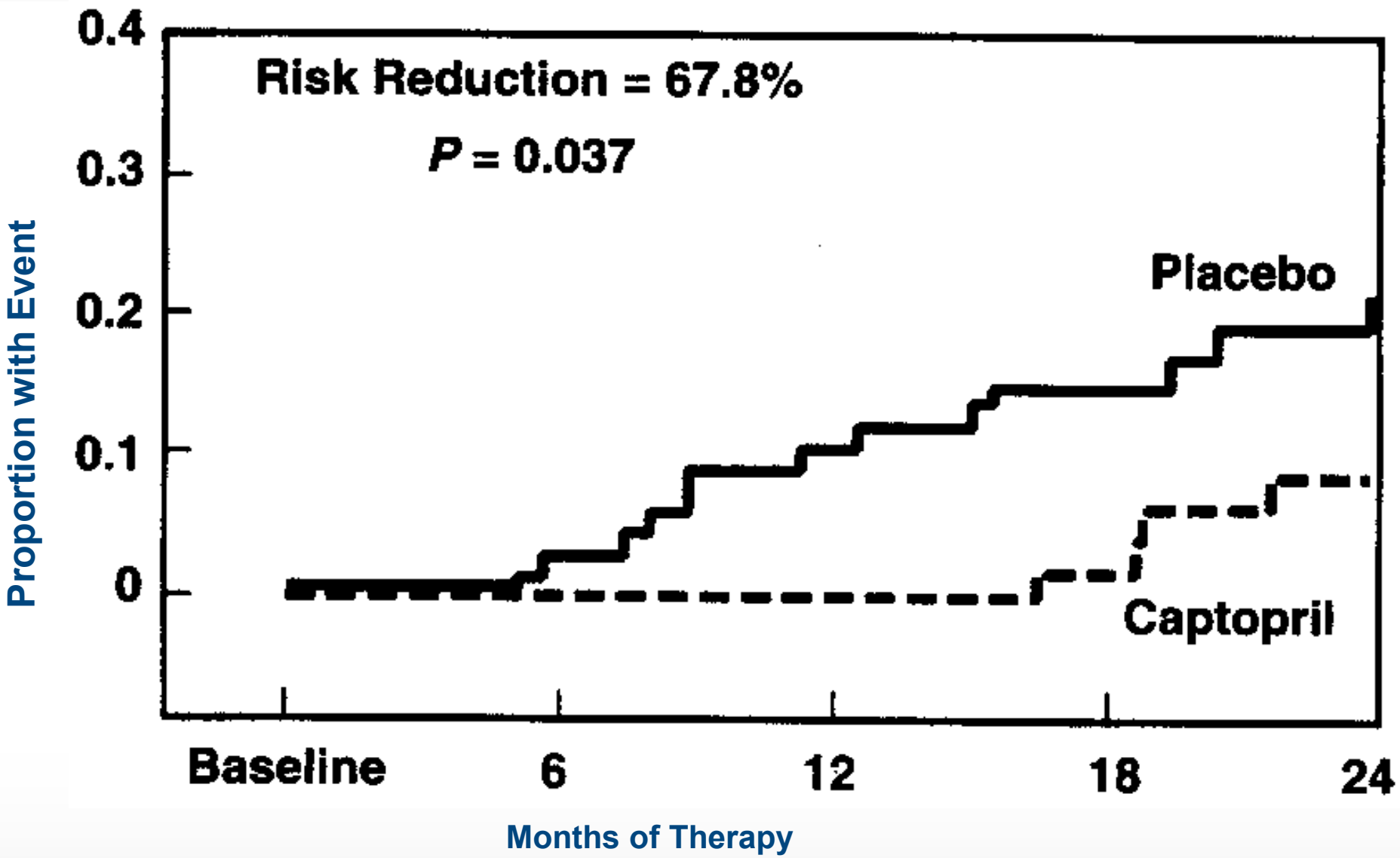
KDIGO recommends that treatment with an angiotensin-converting enzyme inhibitor (ACEi) or an angiotensin II receptor blocker (ARB) be initiated in patients with diabetes, hypertension, and albuminuria, and that these medications be titrated to the highest approved dose that is tolerated.

- Use only one agent at a time to block the RAS. The combination of an ACEi with an ARB, or the combination of an ACEi or ARB with a direct renin inhibitor, is potentially harmful.



Monitoring of serum creatinine and potassium during angiotensin-converting enzyme inhibitor (ACEi) or angiotensin II receptor blocker (ARB) treatment—dose adjustment and monitoring of side effects. AKI, acute kidney injury; NSAID, nonsteroidal anti-inflammatory drug.

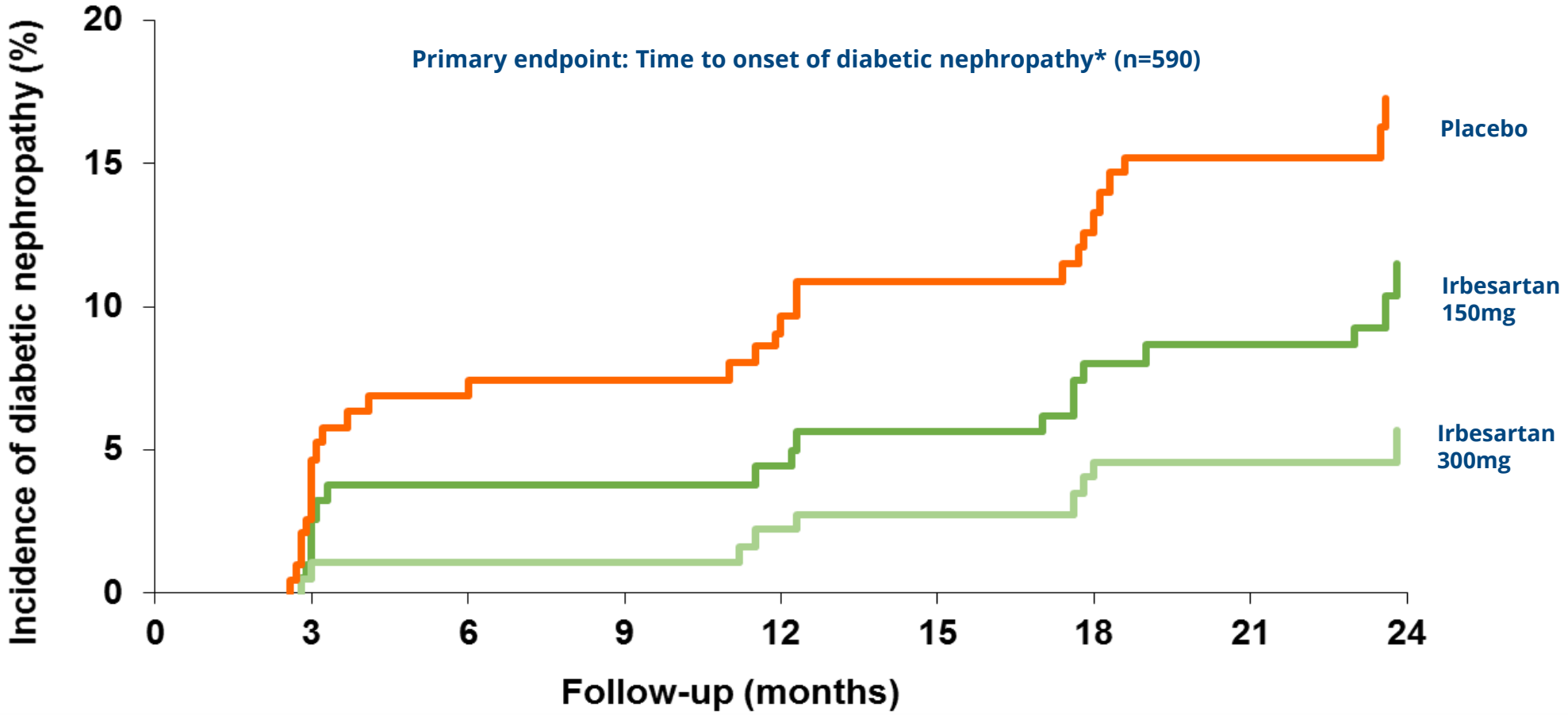
ACE-inhibitor in Type 1 diabetes with MAU Reduces Progression to Clinical Proteinuria



Laffel LM et al. Am J Med 1995;99(5):497-504.

MAU, microalbuminuria

ARB in Type 2 diabetes with MAU reduces progression

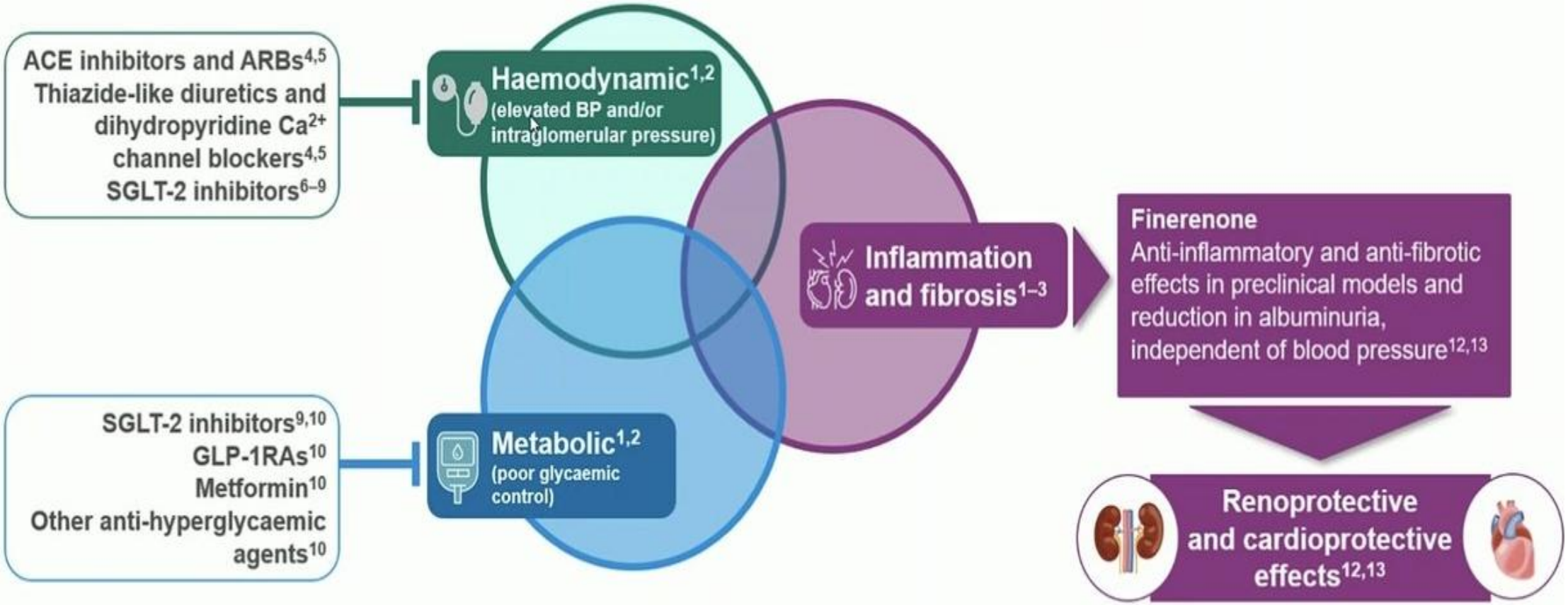


*defined by persistent albuminuria in overnight specimens, with urinary albumin excretion rate <200 µg/min and ≥30% higher than baseline level

Parving et al. *N Engl J Med* 2001;345:870-8

MAU, microalbuminuria

Finerenone is hypothesized to slow CKD progression by directly targeting inflammation and fibrosis

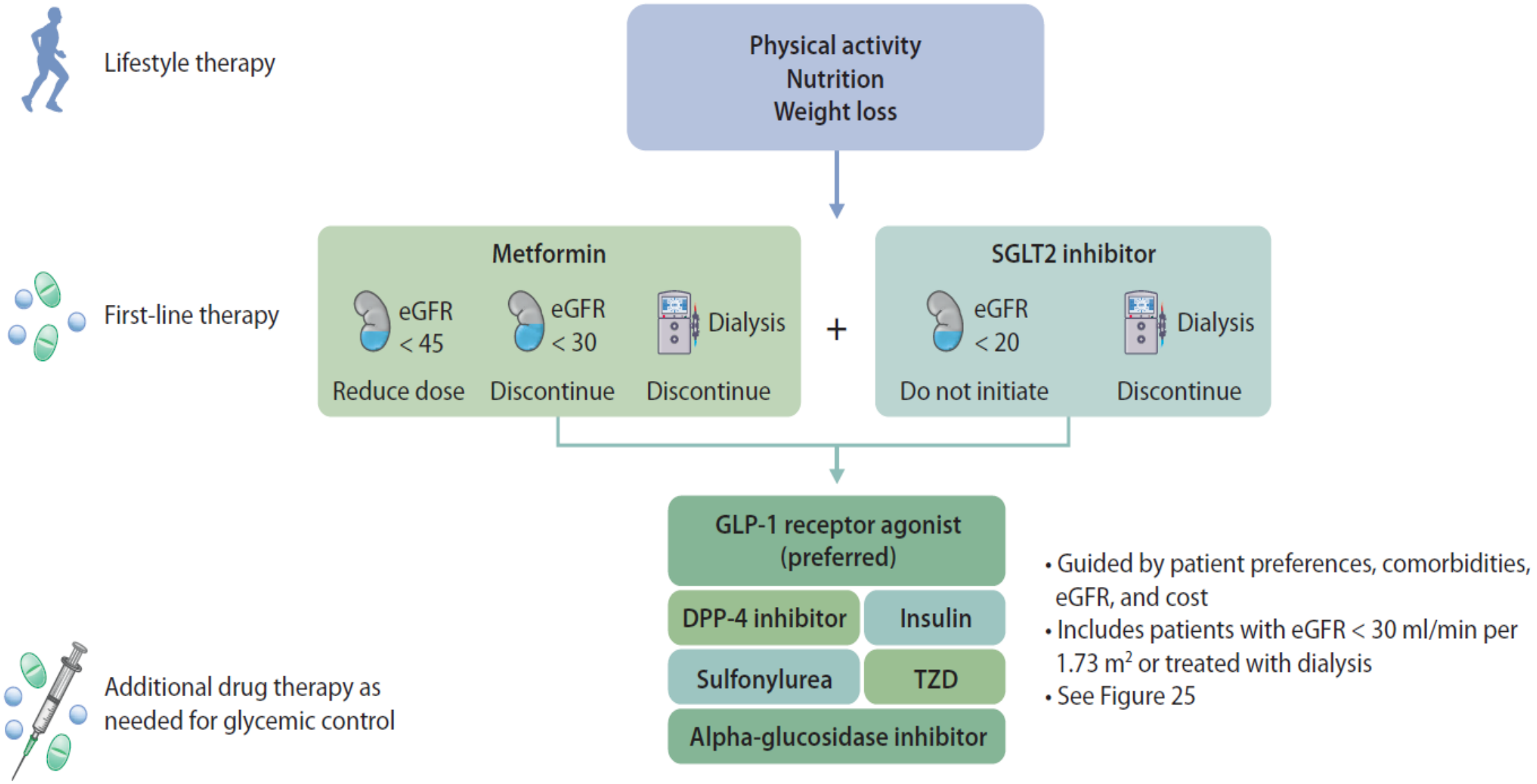


1. Alicic RZ, *et al. Clin J Am Soc Nephrol* 2017;12:2032–2045; 2. Mora-Fernández C, *et al. J Physiol* 2014;18:3997; 3. Bauersachs J, *et al. Hypertension* 2015;65:257–263; 4. American Diabetes Association. *Diabetes Care* 2020;43:S135-151; 5. American Diabetes Association. *Diabetes Care* 2020;43:s111–1340; 6. Kidokoro K, *et al. Circulation* 2019:140;303–315; 7. Zelniker TA & Braunwald E. *J Am Coll Cardiol* 2018;72:1845–1855; 8. Heerspink HJ, *et al. Circulation* 2016;134:752–772; 9. Zelniker TA & Braunwald E. *J Am Coll Cardiol* 2020;75:422–434; 10. American Diabetes Association. *Diabetes Care* 2020;43:S98–S110; 11. Alicic RZ, *et al. Adv Chronic Kidney Dis* 2018;25:1941–191; 12. 6. Kolkhof P, *et al. J Cardiovasc Pharm* 2014;64:69–78; 13. Grune J, *et al. Hypertension* 2018;71:599–608

Recently, 2 large clinical trials have examined the cardiovascular and kidney effects of **finerenone** in those with T2D and albuminuria, enrolling patients with serum potassium levels less than 4.8 mmol/l at screening

	FIDELIO-DKD	FIGARO-DKD
Drug	Finerenone	Finerenone
Total number of participants	5734	7437
% with CVD	45.4	44.7
eGFR and ACR criteria for enrollment	25–<60 ml/min per 1.73 m^2 and ACR 30–<300 mg/g [3–<30 mg/mmol] OR 25–<75 ml/min per 1.73 m^2 and ACR 300–5000 mg/g [30–500 mg/mmol]	25–90 ml/min per 1.73 m^2 and ACR 30–<300 mg/g [3–<30 mg/mmol] OR ≥60 ml/min per 1.73 m^2 and ACR 300–5000 mg/g [30–500 mg/mmol]
Mean eGFR at enrollment (ml/min per 1.73 m^2)	44	68
% with eGFR <60 ml/min per 1.73 m^2	88.4	38.2
Median ACR at enrollment (mg/g [mg/mmol])	850 [85.0]	309 [30.9]
% with ACR ≥300 mg/g (30 mg/mmol)	87.5	50.7
Follow-up time (median, yr)	2.6	3.4
Primary outcome	Kidney composite: kidney failure, a sustained decrease ≥40% in GFR, renal death	CV composite: death from CV causes, nonfatal MI, nonfatal stroke, or hospitalization for HF
Main secondary outcome	CV composite: death from CV causes, nonfatal MI, nonfatal stroke, or hospitalization for HF	Kidney composite: kidney failure, a sustained decrease ≥40% in GFR, renal death
Kidney composite outcome result	HR: 0.82; 95% CI: 0.73–0.93	HR: 0.87; 95% CI: 0.76–1.01
Cardiovascular composite outcome result	HR: 0.86; 95% CI: 0.75–0.99	HR: 0.87; 95% CI: 0.76–0.98

Glucose-lowering therapies



Treatment algorithm for selecting glucose-lowering drugs for patients with type 2 diabetes (T2D) and chronic kidney disease (CKD). Kidney icon indicates estimated glomerular filtration rate (eGFR; ml/min per 1.73 m^2); dialysis machine icon indicates dialysis. DPP-4, dipeptidyl peptidase-4; GLP-1, glucagon-like peptide-1; SGLT2, sodium–glucose cotransporter-2; TZD, thiazolidinedione.

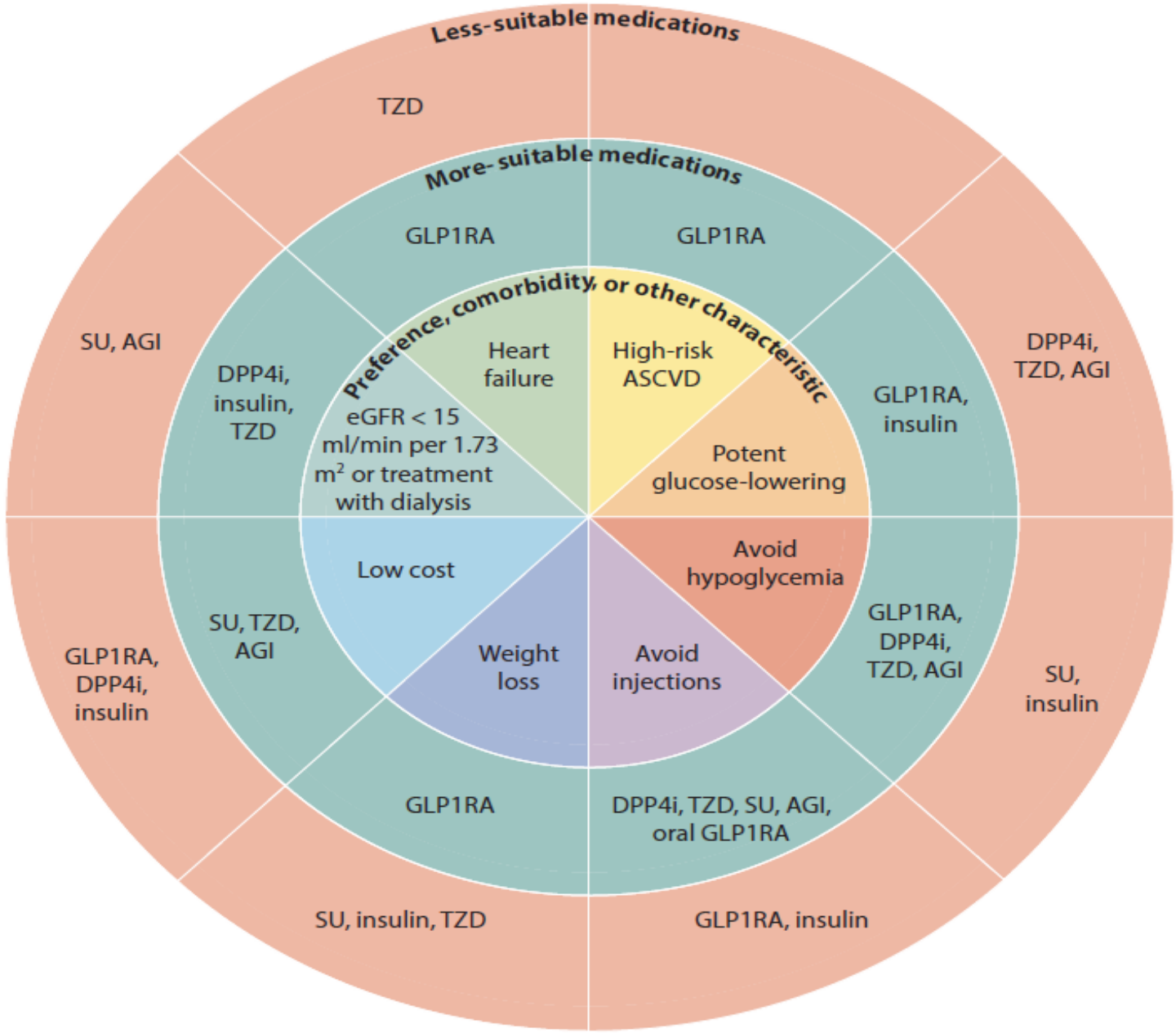
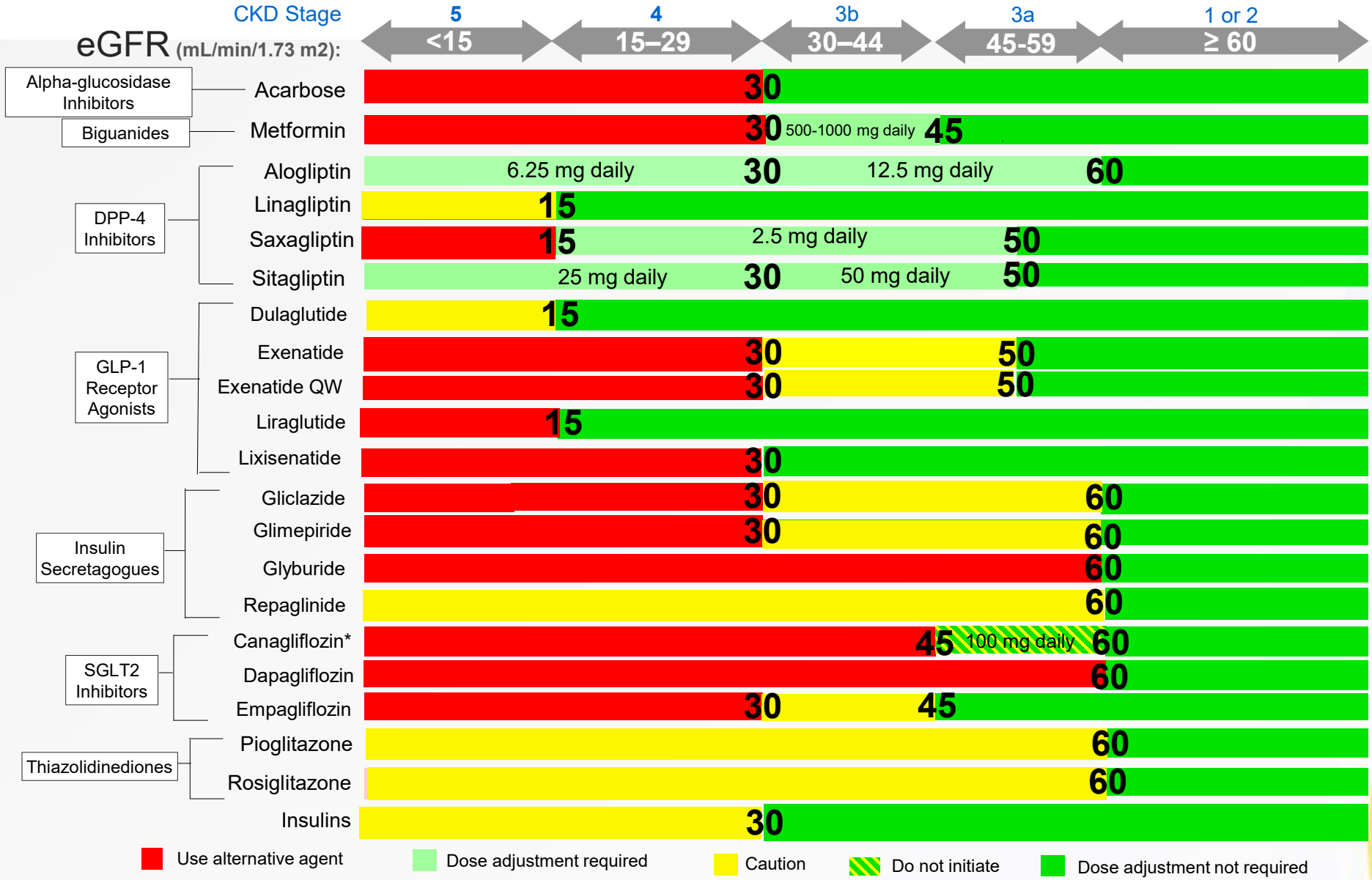


Figure 2. factors influencing the selection of glucose-lowering drugs other than sodium–glucose cotransporter-2 inhibitor (SGLT2i) and metformin in type 2 diabetes (T2D) and chronic kidney disease (CKD). AGI, alpha-glucosidase inhibitor; ASCVD, atherosclerotic cardiovascular disease; DPP4i, dipeptidyl peptidase-4 inhibitor; eGFR, estimated glomerular filtration rate; GLP1RA, glucagon-like peptide-1 receptor agonist; SU, sulfonylurea; TZD, thiazolidinedione.

Antihyperglycemic Agents and Renal Function



** May be used for cardiorenal benefits in those with clinical CVD, A1C above target and eGFR >30 mL/min/1.73m2*

Glucose-lowering therapies in patients with T2D and CKD

- Glycemic management for patients with T2D and CKD should include lifestyle therapy, first-line treatment with both metformin and a sodium-glucose cotransporter-2 inhibitor (SGLT2i), and additional drug therapy as needed for glycemic control.
- Most patients with T2D, CKD, and eGFR ‡30 ml/min per 1.73 m2 would benefit from treatment with both metformin and an SGLT2i.
- Patient preferences, comorbidities, eGFR, and cost should guide selection of additional drugs to manage glycemia, when needed, with glucagon-like peptide-1 receptor agonist (GLP-1 RA) generally preferred.

Antihyperglycemic therapies in patients with type 2 diabetes (T2D) and CKD

Sodium–glucose cotransporter-2 inhibitors (SGLT2i)

- SGLT2i confer significant renoprotective and cardioprotective effects in these patients.
- 3 large RCTs (e.g., the Empagliflozin Cardiovascular Outcome Event Trial in Type 2 Diabetes Mellitus Patients–Removing Excess Glucose [EMPAREG] trial, Canagliflozin cardiovascular Assessment Study [CANVAS], and Dapagliflozin Effect on Cardiovascular Events [DECLARE-TIMI 58] trial) reporting on efficacy for primary cardiovascular outcomes and secondary kidney outcomes.

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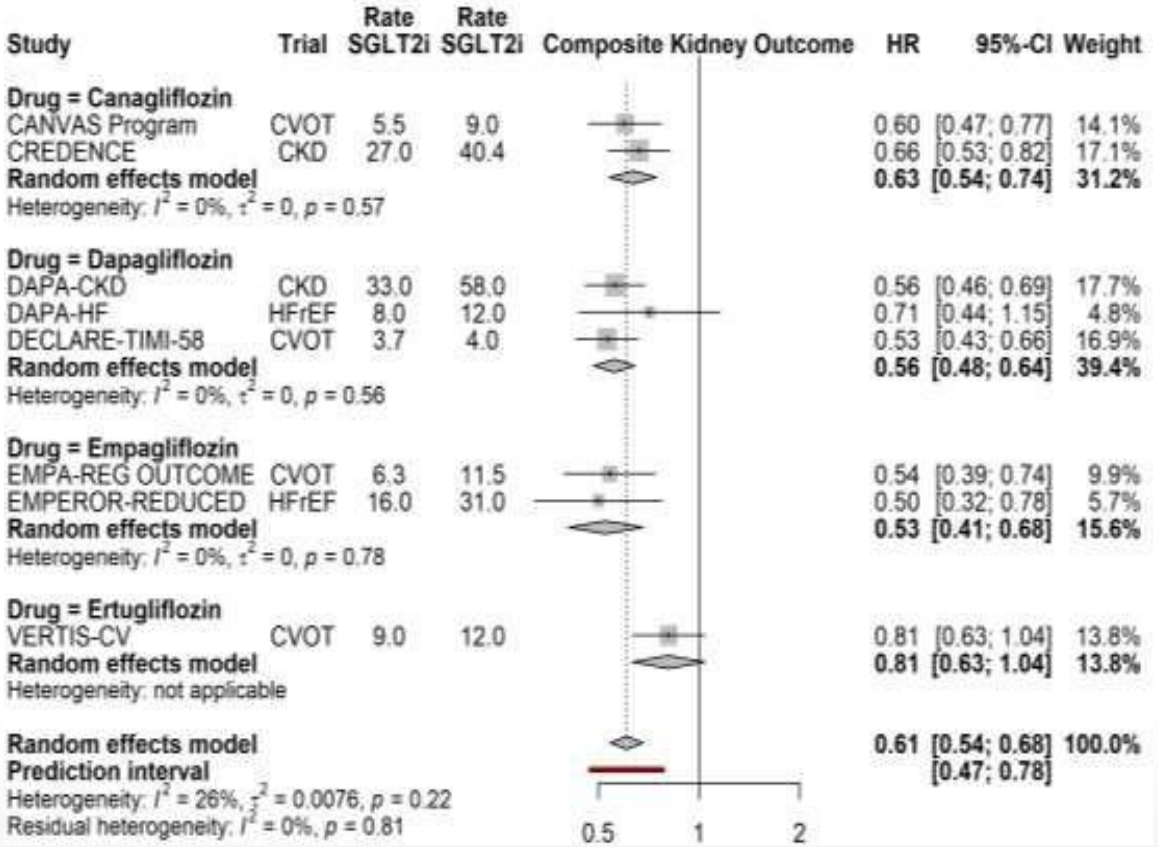
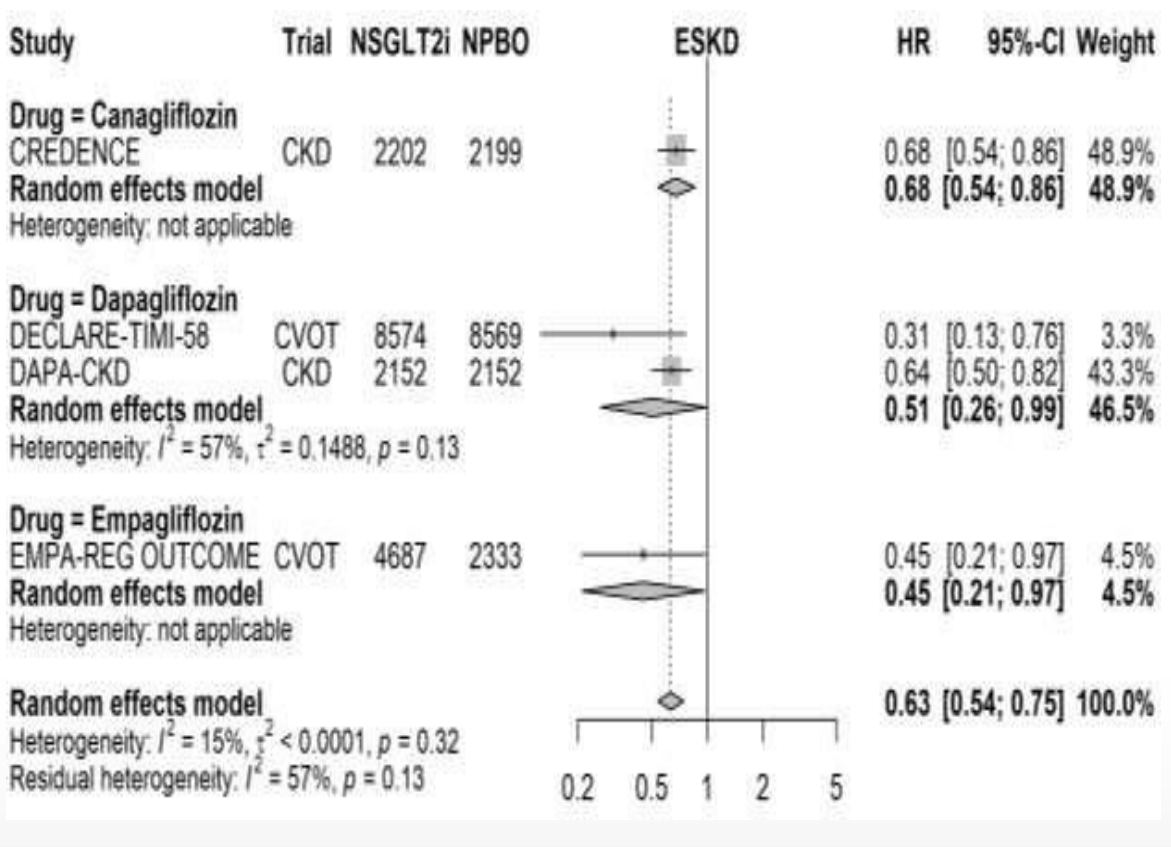
Antihyperglycemic therapies in patients with type 2 diabetes (T2D) and CKD

- SGLT2i lower blood glucose levels by inhibiting kidney tubular reabsorption of glucose. They also have a diuretic effect, as the induced glycosuria leads to osmotic diuresis and increased urine output.

SGLT2i in T2DM Reduces Renal Outcomes

SGLT2i reduced rates of ESKD by 37% and the composite kidney outcome of worsening kidney function/ ESKD by 39%





Sodium–glucose cotransporter-2 inhibitors (SGLT2i)

KDIGO recommends treating patients with type 2 diabetes (T2D), CKD, and an eGFR ‡20 ml/min per 1.73 m2 with an SGLT2i

SGLT2 inhibitor	Dose	Kidney function eligible for inclusion in pivotal randomized trials	Dosing approved by the US FDA
Dapagliflozin	10 mg daily	eGFR ≥25 ml/min per 1.73 m^2 in DAPA-CKD eGFR ≥30 ml/min per 1.73 m^2 in DAPA-HF and DECLARE	eGFR ≥25 ml/min per 1.73 m^2
Empagliflozin	10 mg daily (Can increase to 25 mg daily if needed for glucose control)	eGFR ≥30 ml/min per 1.73 m^2 in EMPA-REG eGFR ≥20 ml/min per 1.73 m^2 in EMPEROR-Reduced and EMPEROR-Preserved	eGFR ≥30 ml/min per 1.73 m^2 for T2D and ASCVD for glucose control eGFR ≥20 ml/min per 1.73m^2 for HF
Canagliflozin	100 mg daily (The higher dose of 300 mg is not recommended for CKD)	eGFR ≥30 ml/min per 1.73 m^2 in CREDENCE	eGFR ≥30 ml/min per 1.73 m^2

Figure 7 | Sodium–glucose cotransporter-2 inhibitors (SGLT2i) with established kidney and cardiovascular benefits and dose adjustments as approved by the US Food and Drug Administration (FDA) (take note of country-to-country variation). ASCVD, atherosclerotic cardiovascular disease; CKD, chronic kidney disease; eGFR, estimated glomerular filtration rate; HF, heart failure; T2D, type 2 diabetes.

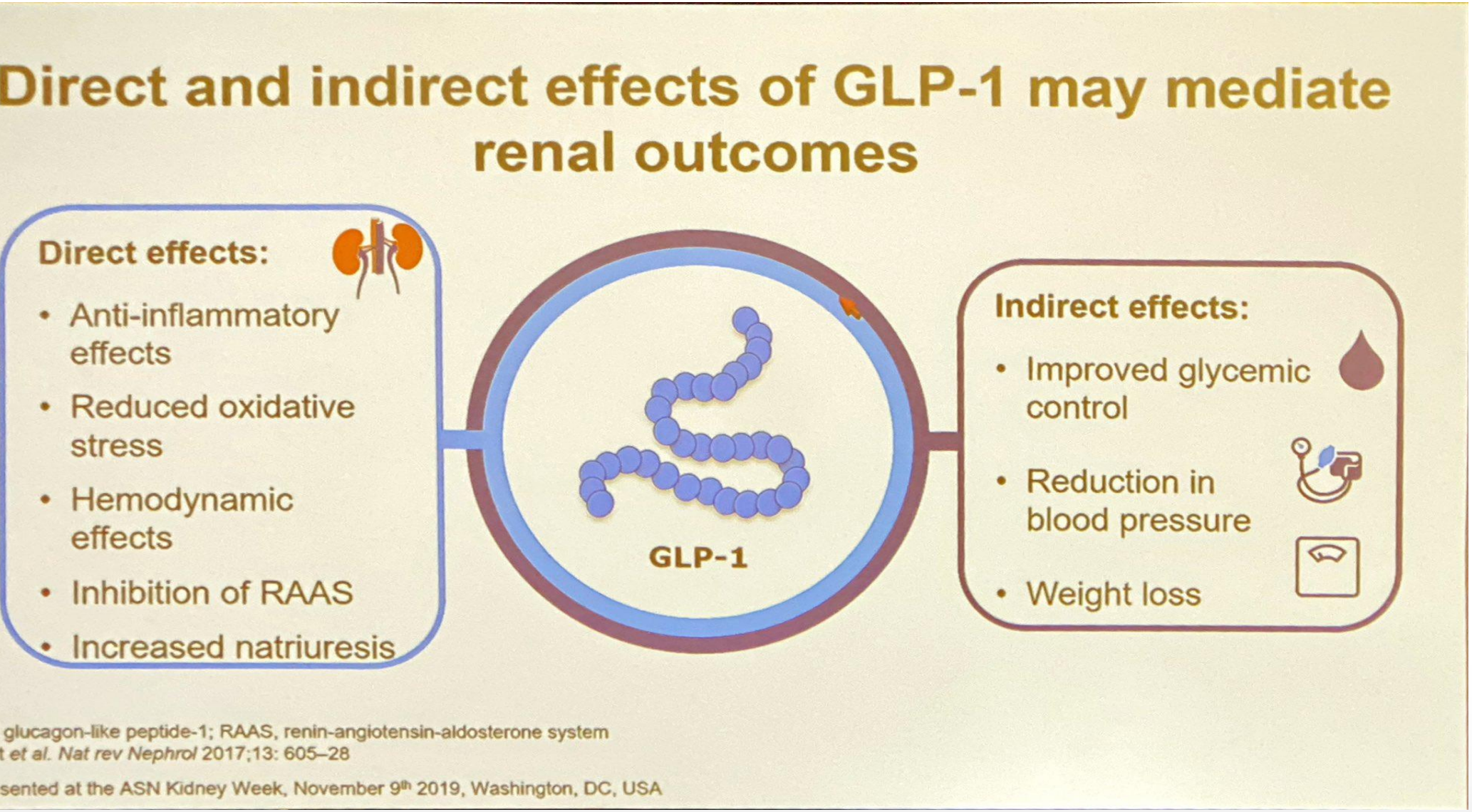
Glucagon like peptide 1(GLP 1) receptor agonists

- GLP1 receptor agonists are injectable subcutaneous medications that stimulate glucose depedent insulin release, decrease glucagon secretion, delay gastric empting and supress appetite,the last may result in significant weight loss.
- They are fairly potent, generally causing a decrease in HbA1c of 0.5 to 1.5%.

Glucagon like peptide 1(GLP 1) receptor agonists

- The LEADER, SUSTAIN-6,and REWIND studies showed significant reduction in CVD mortality with liraglutide, semaglutide and dulaglutide respectively,along with reduction in the development of severe albuminuria but no effect on GFR.
- Neither CVD nor CKD benefits were seen with extended release exenatide or lixisenatide.

Direct and indirect effect of GLP-1 may mediate kidney outcome



GLP-1, glucagon-like peptide-1; RAAS, renin-angiotensin-aldosterone system
Muskiet *et al. Nat rev Nephrol* 2017;13: 605–28

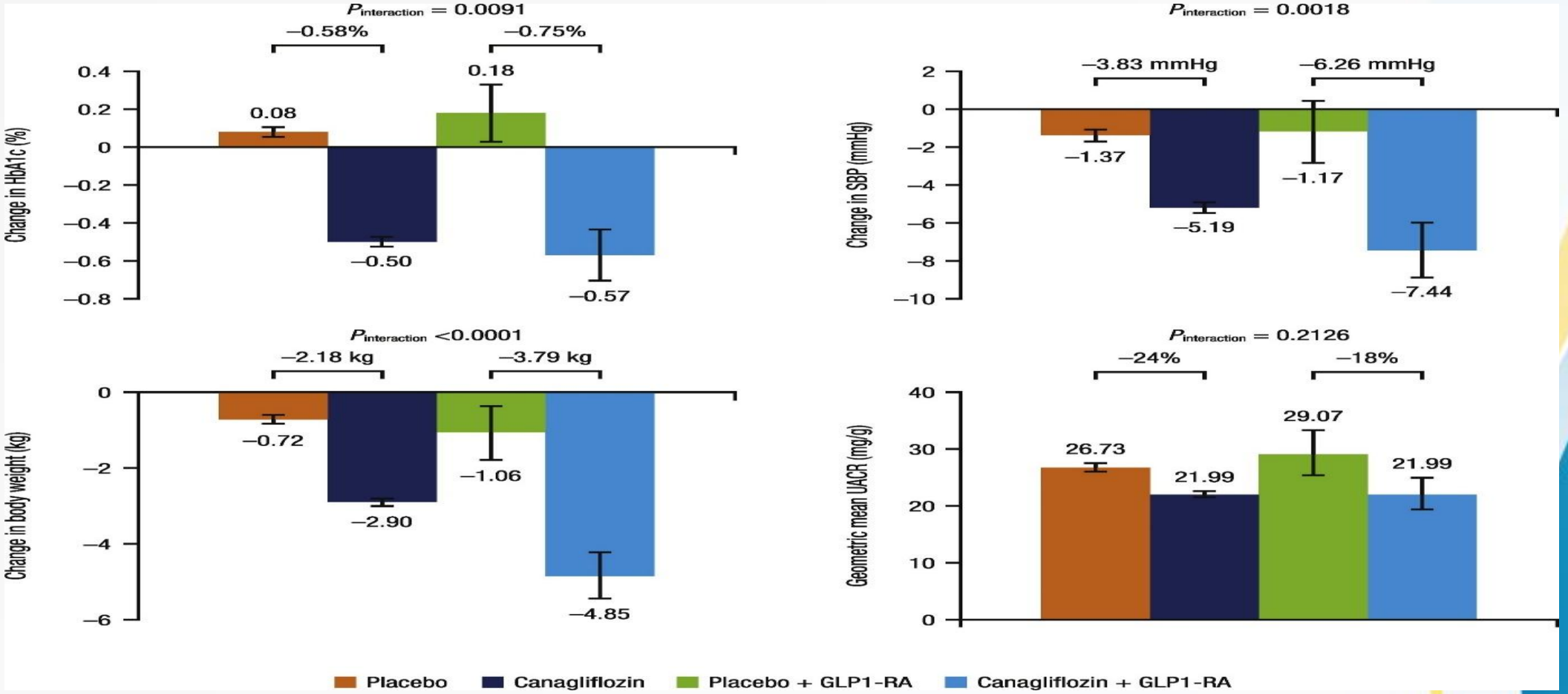
Presented at the ASN Kidney Week, November 9th 2019, Washington, DC, USA

Glucagon-like peptide-1 receptor agonists (GLP-1 RA)

In patients with T2D and CKD who have not achieved individualized glycemic targets despite use of metformin and SGLT2i treatment, or who are unable to use those medications, KDIGO recommends a long-acting GLP-1 RA

GLP-1 RA	Dose	CKD adjustment
Dulaglutide	0.75 mg and 1.5 mg once weekly	No dosage adjustment Use with eGFR >15 ml/min per 1.73 m^2
Exenatide	10 µg twice daily	Use with CrCl >30 ml/min
Exenatide extended-release	2 mg once weekly	Use with eGFR >45 ml/min per 1.73 m^2
Liraglutide	1.2 mg and 1.8 mg once daily	No dosage adjustment Limited data for severe CKD
Lixisenatide	10 µg and 20 µg once daily	No dosage adjustment Limited data for severe CKD Not recommended with eGFR <15 ml/min per 1.73 m^2
Semaglutide (injection)	0.5 mg and 1 mg once weekly	No dosage adjustment Limited data for severe CKD
Semaglutide (oral)	3 mg, 7 mg, or 14 mg daily	No dosage adjustment Limited data for severe CKD

Canvas: adding SGLT2 inhibitors to GLP-1 RA Leads to larger reductions in HbA1C, SBP and body weight than SGLT2 inhibitor alone



Insulin

- About 30% to 80% of insulin clearance is carried out by the kidney.
- A reduction in GFR results in prolongation of the insulin half-life and a need dose adjustment to avoid hypoglycemia.
- All insulin preparations can be used in CKD, but modifications of insulin type and dose may be necessary.
- Careful home glucose monitoring is required to adjust insulin doses safely.

Insulin

Insulin Type	Dose	Onset of action	Peak Hour	Duration of Action	Dose adjustment for avoid hypoglycemia
long-acting insulin analogs					
Glargine	Once Daily	2-4 hours after injection	does not have a clear peak	20 - 24 hours	No Need
Detemir	twice daily	1-3 hours	6-8 hours	18-22 hours	No Need
Degludec	Once Daily	**30–90 min**	does not have a clear peak	Over 24 hours	No Need
Intermediate-acting insulin					
NPH (neutral protamine Hagedorn) insulin	twice daily	2-4 hours	Peak at 4-10 hours, and lasts for up to 10-18 hours	8–12 hours	

Insulin

Insulin Type	Dose	Onset of action	Peak Hour	Duration of Action	Dose adjustment for avoid hypoglycemia
short-acting insulin					
Regular crystalline insulin	Once Daily	30-60 minutes	Peaks at 2-3 hours, and lasts for 5-8 hours	4 – 6 hours	No Need
Rapid acting Insulin					
aspart, lispro, and glulisine	twice daily	about 15 minutes	about 60 minutes	4 hours	No Need
Inhaled insulin	twice daily	12-15 minutes	50 minutes	2.5-3.0 hours	No Need

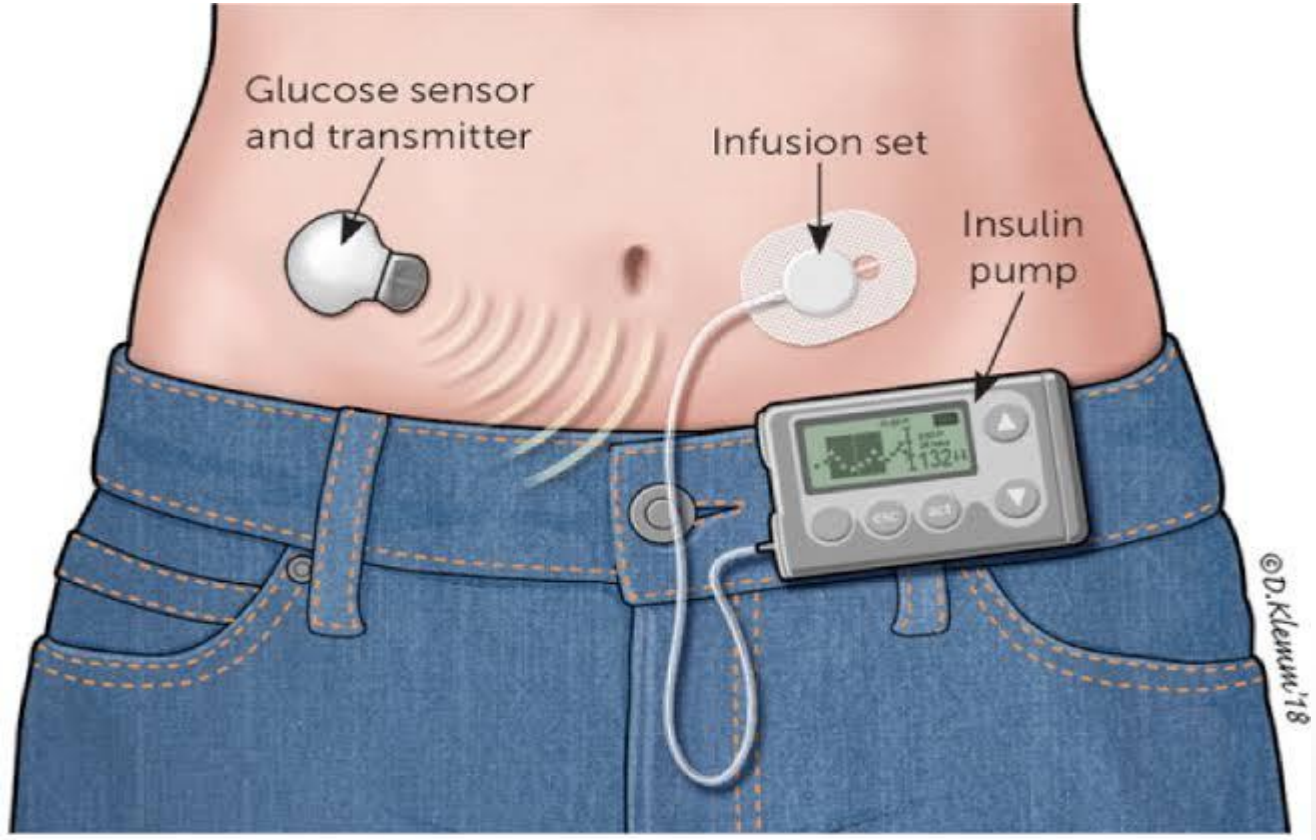
We should use

Although rapid acting insulins are usually injected before eating, some patients with stage 4-5 CKD and on dialysis may delay gastric emptying, so giving these rapid acting insulins after meal may help to match the insulin peak with the time of the postprandial blood glucose peak.

An insulin pump delivers a continuous subcutaneous infusion of insulin provides the closest approximation of physiologic insulin secretion and potentially can be used in all stages of CKD. Rapid acting insulin analogs infused via pump serve as basal, bolus and correction of insulin.

Closed loop insulin delivery system combine the use of an insulin pump and a CGM sensor. The pump and sensor are in communication to automatically decrease, increase or temporarily stop the delivery of insulin in response to the glucose levels.

- U-500 regular insulin, U-300 glarine, U-200 degludec, U-200 lispro are usually used in patients with severe insulin resistance who require high dose insulin and it can be given by subcutaneous injection or in a pump




Thank You